Chapter 3

Pathogenic Role of Cytokines and Effect of Their Inhibition in Psoriasis

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Abstract

The pathogenesis of psoriasis is complex, and cytokines play an important role in mediating cell-cell interactions that result in abnormal structures and functions of many cell types in psoriasis, such as abnormal proliferation and differentiation of keratinocytes, abnormal proliferation of blood vessels, stimulation of immune cells, and driving abnormal immune reactions. In this chapter, we summarize the roles and functions of inflammatory cytokines that play a crucial role in psoriasis such as tumor necrosis factor (TNF)-α, interleukin (IL)-12/IL-23, and IL-17, as well as their inhibitors that are used to treat psoriasis.

Keywords: psoriasis, inflammation, cytokine, biologic drugs, pathogenesis

1. Introduction

Psoriasis is a common chronic inflammatory disease characterized by abnormal proliferation of keratinocytes, increased dermal vascularity, and multiple inflammatory cell infiltration. It is an immune-mediated skin disease influenced by genetic and epigenetic variations, which can be triggered by environmental factors. Psoriasis affects approximately 2% of people worldwide [1, 2].

Psoriasis typically presents as indurated scaly erythematous plaques and is easily diagnosed; however, variable clinical manifestations may be presented. As a result, psoriasis remains a clinical diagnosis defined by morphologic findings and appearances. The major clinical manifestations include characteristic cutaneous lesions, including whitish scaly erythematous plaques and/or pustular or guttate lesions. There are several clinical forms of psoriasis,

including plaque psoriasis, psoriasis guttate, psoriasis arthropathica, pustular psoriasis, psoriasis erythroderma, and inverse psoriasis. The most common type of psoriasis is psoriasis vulgaris, which accounts for 85–90% of all cases [1, 3].

Histologically, psoriasis is characterized by hyperproliferation and abnormal differentiation of keratinocytes; dilated, hyperplastic blood vessels; and inflammatory infiltration of lymphocytes mainly into the dermis. The skin patches are typically erythematous and scaly, which, in addition to the physical appearance, may result in psychological stress and poor quality of life. Like other systemic inflammatory diseases, psoriasis affects far more organs than the skin and often presents with chronic inflammatory responses in joints, nails, and other organs.

Immunological dysfunction in psoriasis involves cross talk between immune cells and non-immune cells with cytokines. Several important types of immune cells in psoriasis have been found to play a role in pathogenesis, including Th1, Th17, and regulatory T cells. Corresponding cytokines that may be involved include interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-23, and IL-17. More recently, IL-9-secreting Th9 cells have been identified, and the inflammatory responses of keratinocytes, γδT cells, T regulatory cells, and other cell types in psoriasis have been explored. Emerging evidence indicates that new genetic variations and epigenetic modifications are associated with psoriatic disease [4, 5].

2. Immunological changes in psoriasis

Psoriasis is characterized by keratinocyte hyperproliferation and the abnormal infiltration of effector T cells, dendritic cells, neutrophils, and macrophages [6]. The effect of multiple cell types involved in psoriasis is mediated by a complex network of cytokines and their interactions.

3. Role of inflammatory cytokines in psoriasis

3.1. Interferons (IFN)

Type I interferons (IFNs), IFN-α and IFN-β, can suppress viral replication and stimulate immune reactions in response to viral infections; thus, they are potential mediators of antiviral host defense. Activated plasmacytoid dendritic cells (pDCs) preferentially produce type I IFNs following interactions between intracellular TLR7 and TLR9 with viral RNA and DNA [7, 8]. Type I IFN-α and IFN-β are not expressed in the normal skin but are produced in virally infected skin where pDCs are present, as well as in skin wounds where mechanical injury stimulates infiltration of pDCs and in lesional psoriatic skin where pDC-derived type I IFNs are sustained [9]. This stimulates myeloid DC phenotypic maturation and activation, enabling T-cell priming. Several studies have demonstrated that these cytokines are most relevant in the early phase of psoriasis, as demonstrated by the IFN-α signature in primary psoriatic plaques. Albanesi et al. [10] found that pDC infiltration in psoriatic skin correlates

with the expression of markers typical of early stage of disease, whereas it is notably absent in chronic lesions. In this regard, blocking of type I IFN signaling may prevent the upregulation of T cells and development of non-lesional to lesional skin [9]. For downstream inflammatory pathways, type I IFNs modulate the production of IFN-γ and IL-17 and are involved in the differentiation and activation of T cells, particularly Th1 and Th17 cells [11] (**Figure 1**).

Th1 cells are a potential source of IFN-γ, a type II interferon. Previously, the Th1 pathway was proposed to be the predominant pathogenic path for psoriasis [12]. Th1 cells, producing IFN-γ, are increased in the psoriatic lesional skin and peripheral blood and can be decreased by effective therapy. However, the potential role of IFN-γ became less important after the identification of a new key cytokine, Th17-producing IL-17 [13]. Selective blockage of IL-23-induced IL-17 leads to full recovery of psoriasis based on clinical, histological, and molecular markers [14].

IFN-γ acts on psoriatic keratinocytes and endothelial cells, leading to the activation and production of antimicrobial peptides (e.g., LL-37 cathelicidin and β-defensins). IFN-γ induces the cross phosphorylation of Janus kinase 1 (JAK1) and JAK3, resulting in the downstream activation of STAT3. Subsequent activation of STAT transcription factors is important for cell growth and is efficient for regulating many genes expressed in psoriatic lesions [15]. IFN-γ promotes the release of cytokines (IL-23, IL-1) and chemokines (CXCL10, CXCL11), as well as the expression of adhesion molecules from DCs, T cells, keratinocytes, and endothelial cells [16], thus promoting the recruitment of inflammatory cells to lesional plaques. Studies suggest that IFN-γ can be used as a biomarker for determining psoriasis severity and therapy evaluation because of the positive correlation between serum IFN-γ levels and PASI scores [17].

However, direct blockage of IFN-γ with a neutralizing antibody in patients with psoriasis was shown to have little or no therapeutic effect, indicating that IFN-γ does not directly participate the psoriasis phenotype [18]. It has been suggested that the IL-12/IFN-γ axis acts to suppress IL-17-modulated tissue injury [19, 20]. Consequently, continued expression of the IL-12/IFN-γ axis in disease while Th17 circuits are inhibited through IL-23 or IL-17 blockage may lead to better suppression and improvement of psoriasis [5].

3.2. TNF-α

TNF-α is involved in many inflammatory cutaneous diseases, including psoriasis. Several different cells can produce TNF-α in the context of skin inflammation, including keratinocytes, macrophages, T cells (Th1, Th17, and Th22 cells), and psoriatic DCs (particularly TIP-DCs) [5, 21, 22]. Several studies showed that circulating levels of TNF-α (in addition to IFN-γ and IL-12) are elevated in psoriasis patients and correlate with severity of disease [23, 24], although different studies have shown varying results [25].

The key effects of TNF-α are regulating the antigen-presenting ability of DCs and stimulation of T-cell infiltration. It has a variety of effects because there are two types of TNF receptors (TNFR), TNFR1 and TNFR2. TNFR1 is expressed on nearly all cell types, whereas TNFR2 is present predominantly on endothelial cells and hematopoietic cells. TNF-α acts in part

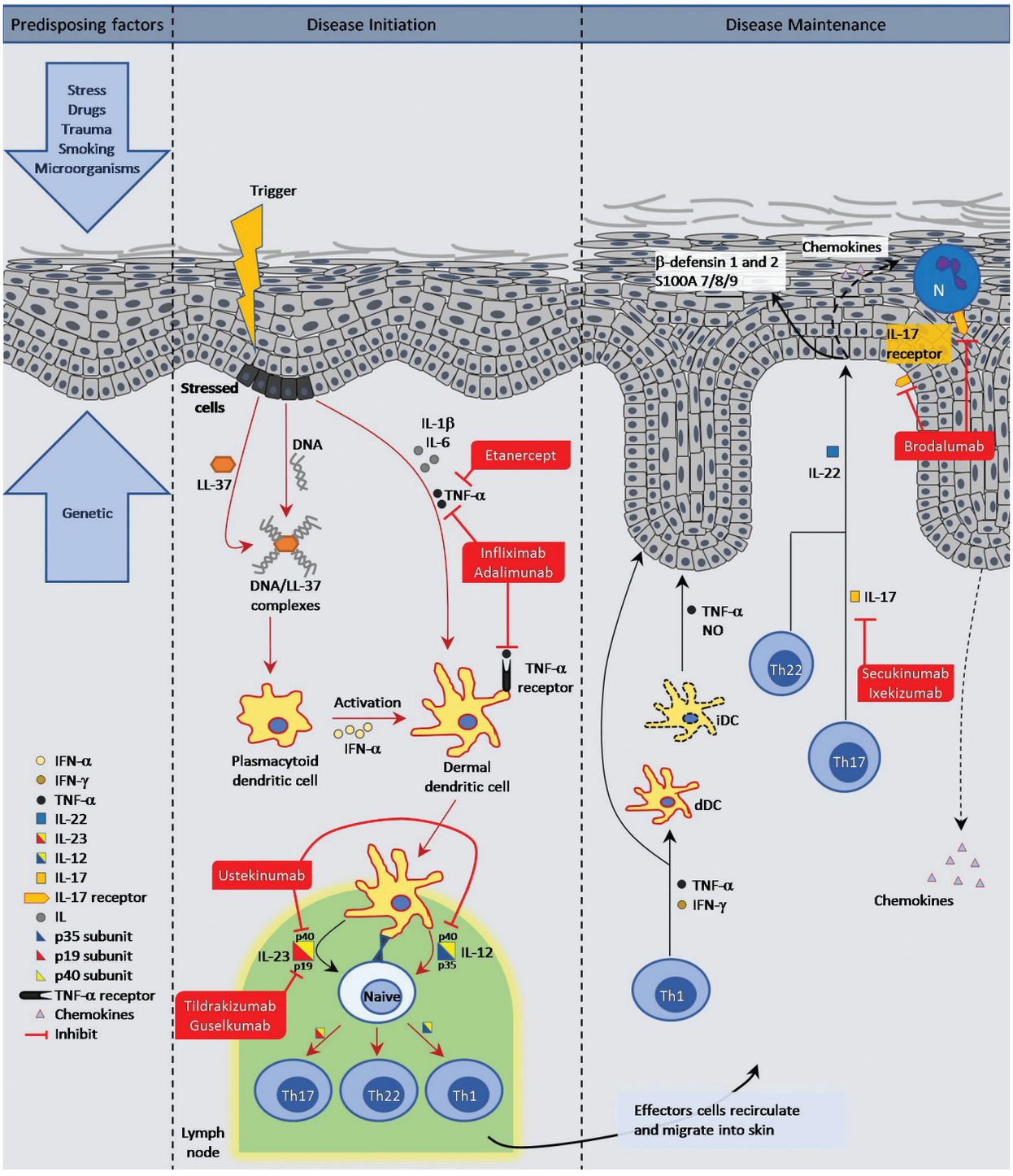

Figure 1. The scheme of cytokine involvement in the pathogenesis of psoriasis and the mechanism of action of biologics.

by increasing the elevated level of active, phosphorylated NF-κB, a crucial transcription factor involved in psoriatic pathogenesis [26]. TNF-α possesses proinflammatory properties; it activates the expression of C-reactive protein (which is a part of the acute phase response) and several cytokines such as IL-6 (which induces keratinocyte hyperproliferation and T-cell proliferation) and IL-23 (which is a potential mediator synthesized from DCs in psoriasis to

stimulate IL-17 production). TNF-α also induces several chemokines including CXCL8/IL-8 (which recruits neutrophil infiltration) and CCL20 (which recruits myeloid DCs and Th17 cells). Therefore, TNF-α is an important regulator of the IL-23/Th17 axis in psoriasis. The multifaceted role of TNF-α has been evaluated in clinical trials of TNF-α antagonists in psoriasis patients, revealing their clinical efficacy [27].

TNF-α-targeting agents were approved for rheumatoid arthritis treatment years before being approved for psoriasis therapy. Inhibition of TNF-α signaling has been broadly used in targeted biological treatment of psoriasis. The three biologics currently approved for the treatment of moderate to severe psoriasis are infliximab, adalimumab, and etanercept (**Table 1**). Effective treatment with TNF antagonists downregulates T-cell and DC numbers and decreases their cytokine levels [27, 28]. Infliximab, a chimeric monoclonal antibody, suppresses TNF-α biologic activity by neutralizing both soluble and membrane-bound forms of TNF-α [29]. Blocking this cytokine activity with infliximab has been demonstrated to rapidly normalize keratinocyte differentiation and reduce the number of epidermal thickness, epidermal T-cell infiltration, and intracellular adhesion molecules of psoriatic plaques, such as e-selectin and VCAM [30–32]. Adalimumab is a fully humanized IgG1 monoclonal antibody [33] that binds with high specificity and affinity to human TNF-α. Adalimumab has been suggested as an effective treatment for moderate to severe chronic plaque psoriasis for up to 12 weeks of therapy [34]. Upon binding to this cytokine, adalimumab neutralizes biologic activities by blocking its interaction with the p55 and p75 cell-surface TNF receptors to inhibit TNF-involved biologic responses [35]. Etanercept, a fusion protein consisting of the extracellular ligand-binding domain of TNF-α receptors and Fc portion of human immunoglobulin G, performs its immune function by neutralizing soluble TNF-α and TNF-β (or known as lymphotoxin-α) [36], which also reduces IL-23, and by suppressing Th17 downstream molecules, including IL-17, IL-22, CC chemokine ligand (CCL) 20, and β-defensin 4 [27]. Particularly, successful treatment was found to be associated with the suppression of genes related to the differentiation and function of Th17 cells. Moreover, inhibition of the IL-23 and Th17 axis led to downregulation of IFN-γ-related genes associated with psoriasis resolution [27, 28]. Furthermore, etanercept can decrease lesional DC expression of co-stimulatory molecules in vitro, impairing DC-T-cell interactions and allogenic T-cell activation [27].

The clinical advantage of TNF-α suppression is related to blockage of the IL-23/Th17 axis. Furthermore, TNF-α and Th17 have been suggested to synergistically stimulate the production of several keratinocyte proinflammatory mediators involved in psoriasis [37]. Therefore, blocking either or both TNF-α and IL-23-Th17 pathways may affect immunopathogenic molecules involved in psoriasis.

Anti-TNF-α therapies for psoriasis are very effective. However, the diverse roles of this cytokine cause various drug-associated adverse effects. Patients treated with these biologic agents show an increased incidence of reactivating latent tuberculosis [38] and emerging serious infections (such as sepsis and opportunistic infections) [39]. Additionally, some studies have linked these anti-TNF drugs, particularly when used in combination with other drugs, to an increased risk of malignancies such as lymphoma [40–42].

Drug name	Drug target	Agent type	Administration	Efficacy (% with PASI 75)	References	Stage of development*
Infliximab (Remicade)	TNF-α	Chimeric TNF-α monoclonal antibody	2-h i.v. infusion (5 mg/kg) at weeks 0, 2, and 6 and then every 8 weeks	75–88 at 10 weeks	Gottlieb et al. [31]; Reich et al. [29]; Menter et al. [106]	Approved
Adalimumab (Humira)	TNF-α	Humanized TNF-α monoclonal antibody	s.c. 80 mg at week 0 and then 40 mg every 2 weeks	53–80 at 12 weeks	Gordon et al. [34]; Menter et al. [35]; Saurat et al. [107]	Approved
Etanercept (Enbrel)	TNF-α	Soluble TNF-α receptor-igg fusion protein	s.c 50 mg every 2 weeks for 3 months and then 50 mg weekly	47–49 at 12 weeks	Leonardi et al. [108]; Papp et al. [36]; Tyring et al. [109]	Approved
Ustekinumab (Stelara, CNTO1275)	p40 subunit of IL-12/IL-23	Humanized p40 monoclonal antibody	s.c. (1) 45 mg or (2) 90 mg weekly for 12 weeks	(1) 66.7–67.1 or (2) 66.4–75.7 at 12 weeks	Leonardi et al. [51]; Papp et al. [50]	Approved
Briakinumab (ABT-874)	p40 subunit of IL-12/IL-23	Humanized p40 monoclonal antibody	s.c. 200 mg at weeks 0 and 4 and then 100 mg at week 8	80.6–81.9 at 12 weeks	Gordon et al. [52]; Gottlieb et al. [53]; Strober et al. [54]	Terminated
Tildrakizumab (MK-3222)	p19 subunit of IL-23	Humanized p19 IgG1 monoclonal antibody	s.c (1) 5 mg or (2) 25 mg or (3) 100 or (4) 200 mg at weeks 0 and 4 and then every 12 weeks thereafter	(1) 33.3 or (2) 64.4 or (3) 66.3 or (4) 74.4 at 16 weeks	Papp et al. [58]	Phase III studies ongoing
Guselkumab (CNTO1959)	p19 subunit of IL-23	Humanized p19 IgG1 monoclonal antibody	s.c (1) 5 mg at weeks 0 and 4 and then every 12 weeks thereafter or (2) 15 mg every 8 weeks or (3) 50 at weeks 0 and 4 and then every 12 weeks thereafter or (4) 100 mg at weeks 0 and 4 and then every 12 weeks there after (5) 200 mg at weeks 0 and 4 and then every 12 weeks thereafter	(1) 44 or (2) 76 or (3) 81 or (4) 79 (5) 81 at 16 weeks	Gordon et al. [59]	Finished phase III trial
Secukinumab (Cosentyx, AIN457)	IL-17A	Humanized IL-17A IgG1 monoclonal antibody	s.c. (1) 150 mg or (2) 300 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks	(1) 67–71.6 or (2) 77.1–81.6 at 12 weeks	Langley et al. [68]	Approved

*State of development in the United States, as of January 2017.

Table 1. Biologic drugs for moderate to severe psoriasis at 10–16 weeks.

3.3. IL-12/IL-23

IL-12 and IL-23 are heterodimeric pleiotropic proteins that share a common p40 subunit (encoded by IL12B) and are thought to be essential for controlling the differentiation of Th1 and Th17 cells, respectively. The second distinct subunit of IL-12 is the p35 subunit, and the second unique subunit of IL-23 is the p19 subunit (encoded by IL23A). Expression of the p19 and p40 subunits was found to be significantly increased in psoriatic skin lesions, while the p35 subunit was not [43, 44], suggesting that IL-23 is important in the pathogenesis of psoriasis. Further support from clinical trials revealed that the expression of IL-12/IL-23 was decreased following psoriasis treatment [45–47]. IL-23 and IL-12 are primarily secreted by DCs and macrophages and play a crucial role in psoriatic pathogenesis by regulating Th17 and Th1 cells, including the activation and differentiation of effector T cells, stimulation of keratinocytes, and upregulation of TNF-α expression in psoriatic plaques [43, 48]. IL-23 binds to IL-23R, which is correlated with Jak2 and Tyk2. Binding of its receptor stimulates a signaling circuit via STAT3 activation.

Anti-IL-12/IL-23 and anti-IL-23 drugs are highly effective treatments for psoriasis (**Table 1**) [49]. Recently, the only published results from clinical trials describe two agents of the p40 subunit inhibitors, ustekinumab and briakinumab. Ustekinumab is a human IgG1 monoclonal antibody that neutralizes the shared p40 subunit of IL-12 and IL-23. The agent prevents the interaction of IL-23 and IL-12 with their cell-surface receptors, blocking the Th17 and Th1 signaling cascades. It has been demonstrated to be efficacious for moderate to severe psoriasis [50, 51]. Clinical trials showed that another fully human anti-IL-12/IL-23p40 monoclonal antibody, briakinumab, was also efficacious for the disease [52–54]. However, after phase III trials, safety results concerning a possible increased risk of major adverse cardiovascular events (myocardial infarction, cerebrovascular accident, and cardiac death) with the use of briakinumab let to cessation of its development and withdrawal of the application in 2011 [55, 56].

The structurally related p19 subunit of IL-23 has recently emerged as an attractive target for moderate to severe psoriasis treatment, although these drugs have not been FDA approved [57]. Several agents targeting the p19 subunit are under investigation in clinical trials. Tildrakizumab is a humanized IgG1κ that binds to the unique p19 subunit of IL-23 [58]. This agent was effective in treating moderate to severe plaque psoriasis in a phase IIb clinical trial. Phase III studies are currently underway. Similarly, phase III trials of another fully human IgG1λ monoclonal p19 antibody, guselkumab, are currently a success [59].

3.4. IL-17

IL-17, the main cytokine effector of Th17 cells, is an important cytokine in the pathogenesis of psoriasis. Neutrophils, mast cells, and natural killer (NK) cells also produce IL-17. It is thought to be a proximal regulator of psoriatic cutaneous inflammation and plays a key role in bridging the innate and adaptive immune responses. The IL-17 family comprises six subsets of homo- and heterodimeric cytokines: IL-17A, IL-17B, IL-17C, IL-D, IL-17E, and IL-17F. IL-17A and IL-17F are regarded as the most relevant subtypes in psoriasis. IL-17 is widely thought to be a direct regulator that stimulates keratinocyte proliferation and inhibits keratinocyte

differentiation via the antimicrobial protein REG3A, a mediator with antimicrobial functions involved in wound repair [60]. IL-17 mRNA and protein levels are upregulated in lesional psoriatic plaques and/or blood samples from patients [61, 62]. Lowes et al. [63] demonstrated that psoriatic T cells generate large amounts of IL-17 ex vivo, but T cells from the normal healthy skin did not produce IL-17 under the same conditions.

Keratinocytes are the main target of IL-17A in psoriasis. The IL-17 receptor (IL-17R; consisting of two IL-17RA subunits complexed with one IL-17RC subunit) is expressed on the surface of keratinocytes throughout the epidermis and on scattered dermal cells (DCs, dermal fibroblasts, and endothelial cells) in the psoriatic skin [64]. The interaction between IL-17A and its receptor leads to the production of antimicrobial peptides (AMPs); proinflammatory cytokines such as IL-1, IL-6, IL-23, and IL-19; chemokines; and mediators of tissue injury [62].

IL-17A stimulates the expression of AMPs, including β-defensin and S100A family members, and thus activates the innate immune system [64]. A previous study demonstrated that IL-17A activates the production of multiple chemokines, including CCL20, CXCL1, CXCL2, CXCL3, CXCL5, and CXCL8/IL-8 [37, 64–66]. In addition to stimulating the recruitment and activation of neutrophils, IL-8 acts as a chemotactic factor for NK cells and T cells. CCL20 from human keratinocytes may direct the recruitment of CCR6-positive cells to the skin. Most Th17 cells express CCR6. Therefore, keratinocytes activate Th17-cell recruitment and increase the production of IL-17, promoting a positive feedback loop that maintains the inflammatory disease response [65, 67]. Moreover, CCL20 combined with ICAM-1 can facilitate the recruitment of DCs and T cells in psoriasis. IL-17A and TNF-α act synergistically on psoriatic keratinocytes, causing further production of TNF-α and other proinflammatory mediators.

Several drugs are available or under development that target IL-17 and its pathway. The potential role of the IL-17 pathway has been revealed in psoriatic clinical trials, which showed dramatic improvement. Secukinumab and ixekizumab are humanized IgG1κ and IgG4 monoclonal antibodies that bind and neutralize the IL-17A cytokine. [68, 69]. Secukinumab was approved by the FDA for moderate-to-severe treatment psoriasis in January 2015. In phase III studies, double-blind, 52-week trials, this agent achieved a PASI75 in 67.0–71.6% of patients at a 150-mg dose and 77.1–81.6% of patients with a 300-mg dose (**Table 1**) [68]. The common adverse effects associated with this agent are headache, nasopharyngitis, and upper respiratory tract infections, which are similar to those of other biologics. Ixekizumab, a monoclonal antibody specific for IL-17A, has been shown to be effective for treating psoriasis [70]. This biologic inhibits the expression of cytokines and chemokines involved in the IL-17 pathway [71]. Ixekizumab complete responses were observed in 30.8–35.0% of psoriasis patients and PASI90 in 59.7–65.3% after 12 weeks [69]. These results agree with recent findings that IL-17-producing cells are clearly present in the inflammatory infiltrate. Similar to prior biologic agents, the most commonly reported side effects were nasopharyngitis and injection site reactions. No serious adverse effects were observed [72]. Brodalumab, a unique fully human monoclonal antibody targeting the IL-17 receptor A (IL-17RA), is the newest biologic that has been FDA approved for psoriasis treatment. It binds with high affinity to IL-17RA and blocks the biological activity of IL-17A, IL-17F, and IL-25 (IL-17E), suppressing the downstream effect of IL-17 [73, 74]. In phase III trials to treat psoriasis, brodalumab achieved PASI75 in 83–86%

of patients with a 210-mg dose and 60–69% of patients with a 140-mg dose and PASI 90 in 69–70% after 12 weeks [75, 76]. The most common side effects were nasopharyngitis, upper respiratory infection, and injection site erythema [74]. Based on published results, drugs targeting IL-17 appear to have highly positive effects in moderate-to-severe psoriasis patients with no serious major side effects. Nevertheless, longer-term studies are needed.

3.5. IL-22

IL-22 belongs to the IL-10 family of cytokines, and its receptor (IL-22R) is a complex of two chains (IL-10R and IL-22RA1), which are exclusively expressed on epithelial cells such as keratinocytes [77]. Elevated levels of IL-22 mRNA in the lesional skin of psoriasis and serum IL-22 have been observed [78–80]. Its expression is also decreased after treatment with anti-psoriatic agents [80]. IL-22, produced from Th22 and Th17 cells, induces keratinocyte hyperproliferation, differentiation, migration, and dermal infiltration through STAT3 activation in vivo and in vitro [81]. It also mediates proinflammatory cytokine and AMP production [78, 82].

IL-22 in the human skin can stimulate keratinocytes in various ways. Combined with IL-17, IL-22 can induce AMP production by keratinocytes [83] and parakeratosis and acanthosis by increasing keratinocyte proliferation and inhibit keratinocyte differentiation during part of the tissue-remodeling phase of wound repair, which are observed in psoriasis [84].

Zheng et al. [81] reported that IL-23-induced epidermal hyperplasia in a murine model of psoriasis was dependent on IL-22, and blocking IL-22 in vivo or genetic deletion resulted in downregulation of IL-23-mediated epidermal hyperplasia. Therefore, the important association between the IL-23/Th17 axis and IL-22/Th22 is supported by these studies. However, trials of a human monoclonal antibody targeted against IL-22, fezakinumab, were discontinued because initial processes revealed that the efficacy endpoint could not be achieved [85]. The negative data from these studies suggest that this cytokine is not as critical to psoriasis immunopathogenesis as had initially been considered in earlier studies.

3.6. IL-9

IL-9 is a member of the IL-2 cytokine family. Singh et al. demonstrated markedly elevated expression of IL-9 in the lesional skin of psoriasis patients compared to control subjects. They found increased IL-9R and IL-9 expression in the psoriatic skin and observed a Th17-related inflammatory response after intradermal IL-9 injection in a mouse model [86]. IL-9 is a proinflammatory cytokine that stimulates the production of IL-17, IL-13, IFN-γ, and TNF-α in psoriasis. Both Th9 and Th17 cells are sources of IL-9.

3.7. IL-33

Interleukin-33 is a recently discovered mediator of the IL-1 family [87]. IL-33 mRNA is constitutively expressed in several tissues but is predominantly distributed in epithelial cells, keratinocytes, fibroblasts, DCs, smooth muscle cells, and macrophages. Interestingly, IL-33 specifically localizes to the nucleus of endothelial cells along the vessels and epithelial cells of tissue exposed to the environment [88–90].

The IL-33 receptor is selectively expressed on various cell types, including T-helper-cell (Th) type 2, mast cells, eosinophils, basophils, dendritic cells, group 2 innate lymphoid cells, keratinocytes, and invariant NKT cells [87, 91–94].

IL-33 can act both as a released cytokine, activating ST2L, and as a nuclear-binding factor, regulating gene transcription [95, 96]. Balato et al. [97] showed that IL-33 is present in both the nucleus and cytoplasm of psoriatic keratinocytes. The structure of IL-33 has been determined, and it exhibits the ability to act both as an extracellular cytokine stimulating the ST2L receptor and an intracellular factor controlling gene transcription. However, the role of IL-33 in psoriasis remains unclear.

Many recent studies have shown that IL-33 expression is increased in the lesional skin of psoriasis compared to the normal skin [91, 97, 98]. Hueber et al. [99] demonstrated that IL-33 and ST2 expression are upregulated in human lesional psoriatic plaques compared to the perilesional and normal healthy skin. Moreover, IL-33 is strongly expressed in the nuclei of keratinocytes in psoriasis, which is considered to be a Th1- and Th17-mediated disease, compared with atopic dermatitis which is a Th2-related disease and lichen planus which is related to Th1 cells [96]. We previously demonstrated that IL-17A induces IL-33 expression in normal human epidermal keratinocytes, suggesting that IL-17 in the lesional skin of psoriasis can induce IL-33 expression in the epidermis [91].

Relatively few studies have demonstrated the pathogenic association between IL-33 and psoriasis. Suttle et al. [100] reported decreased IL-33 immunostaining in biopsies in Koebner-positive psoriasis patients, which can reflect the release of IL-33 after skin injury by tape stripping. Interestingly, the proinflammatory cytokine TNF-α dose- and time-dependently activated IL-33 mRNA expression in normal skin cultures ex vivo. Similarly, TNF-α may stimulate the gene expression of IL-33 in normal human epidermal sheets and psoriatic skin [101]. Moreover, the levels of IL-33 were significantly reduced after TNF-α inhibitor therapy [101, 102].

Furthermore, Mitsui et al. [103] recently found that serum IL-33 levels are significantly elevated in patients with psoriasis and are particularly correlated with serum TNF-α levels; this elevation was decreased after anti-TNF-α treatment. They suggested that IL-33 is a general indicator of inflammation in psoriasis. In contrast, Tamagawa-Mineoka et al. [104], Balato et al. [97], and Talabot-Ayer et al. [105] did not detect serum IL-33 expression in psoriasis patients.

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